REMARKS

Claims 22-26 are pending in this application.

Applicants thank the Examiner for withdrawing the objections to the specification and Oath/Declaration in the Office action mailed August 18, 2006. Applicants also thank the Examiner for withdrawing the rejection of claims 22-26 under 35 U.S.C. 112, second paragraph as being indefinite.

Amendment of the Title:

Applicants herein respectfully request amendment of the title by deleting the original title and replacing it with the following title, as suggested by the Examiner in the Office action mailed 2/27/2006: "Method for Diagnosing Lung and Colon Cancer Using PRO357 Specific Antibodies." Applicants respectfully submit that this ground of rejection is overcome and respectfully request that it be withdrawn.

Rejection under 35 U.S.C. § 101:

Claims 22-26 stand rejected under 35 U.S.C. §101 as allegedly not supported by either an asserted utility that is specific and substantial or by a well-established utility. Specifically, the Office action asserts two bases for rejecting the present claims. First, the Office action asserts that one of ordinary skill in the art would not know how to use PRO357 polypeptides or antibodies thereto because "no information is provided in the gene amplification data regarding level of expression, activity, or role in cancer of the PRO357 polypeptide." Page 3 of the Office action mailed 8/18/06. Second, the Office action alleges that the utility requirement is not satisfied because "the specification provides no guidance to enable the skilled artisan to use data relating to PRO357 polypeptide expression in any practical way." Page 9 of the Office action mailed 8/18/06.

Applicants respectfully maintain that claims 22-26 are supported by the specific and substantial utility asserted at page 119 of the specification: " PRO357- . . . encoding genes are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. Amplification is associated with overexpression of the gene product, indicating that

. . . [t]herapeutic agents may take the form of antagonists of . . . PRO357 . . . polypeptide, for example, murine-human chimeric, humanized or human antibodies against a . . . PRO357 . . . polypeptide. These amplifications also are useful as diagnostic markers for the presence of a specific type of tumor type." *See also* page 137. Indeed, as written, the claims clearly are directed to utilizing antibodies that bind PRO357 to diagnose lung or colon cancer. As noted previously, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

The Office action asserts that one skilled in the art would question the objective truth of Applicants assertions of utility at pages 119 and 137 because the specification does not provide explicit evidence that amplification of the PRO357 polynucleotide correlates with overexpression of the PRO357 polypeptide. However, Applicants maintain that explicit evidence is not required to demonstrate an adequate utility. Indeed, according to the MPEP § 2107.02:

> The MPEP does not require an applicant to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980) (reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court pointed out that a rigorous correlation is not necessary when the test is reasonably predictive of the response). See also *Rey-Bellet v. Englehardt*, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974) (data from animal testing is relevant to asserted human therapeutic utility if there is a "satisfactory correlation between the effect on the animal and that ultimately observed in human beings"). Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.

Furthermore, the evidence previously submitted and the declaration of Randy Scott, Ph.D., which is submitted herewith (and discussed below), clearly demonstrates: (1) in

general, it is more likely than not that gene amplification correlates with protein overexpression; and (2) the utility of PRO357 polypeptides and antibodies, asserted in the specification at pages 119 and 137, does not contravene any scientific principles or beliefs. No more is required under 35 U.S.C. § 101 according to the MPEP, *see e.g.* § 2107.02.

Thus, Applicants respectfully submit that one of ordinary skill in the art would know how to use PRO357 polypeptides and antibodies based on the utilities asserted at pages 119 and 137 of the specification and application of the art recognized principle that more likely than not gene amplification correlates with protein overexpression to the demonstrated gene amplification of PRO357.

1. PRO357 gene amplification and protein overexpression

The Office action maintains that a *prima facie* case of lack of utility is established because given the lack of explicit data confirming PRO357 protein overexpression, one of skill in the art would question the objective truth of the statement that gene amplification of PRO357 polynucleotides correlates with protein overexpression of PRO357 polypeptides. Applicants respectfully disagree. Although Applicants respectfully disagree (for the reasons discussed in previous responses, including the response mailed May 30, 2006) that a *prima facie* case of lack of utility is established, Applicants herein argue that even if a *prima facie* case of lack of utility is established, it is overcome when the evidence is considered in its totality, as it must be. Specifically, the totality of the evidence demonstrates that the asserted utility does not contravene any established scientific principles or beliefs. Rather, the totality of the evidence, which includes the Scott, Goddard, and Polakis Declarations, references cited by Applicants including Pollack, Orntoft, Hyman, Bermont, Varis, Hu, Papotti, Walmer, Janssens, Hahnel, Kammori, Bea, Maruyama, and Futcher, and references cited by the Office including Pennica, Konopka, Chen, Hu, LaBaer, Haynes, Gygi, Lian, Fessler, and Hanash, demonstrates that the asserted utility is supported by established scientific principles and beliefs. Most importantly, the totality of the evidence demonstrates that

the asserted utility is supported by the established scientific belief and principle that in general gene amplification correlates with protein overexpression.

Submission of a declaration that either supports the basis or logic of an Applicants' assertion of utility or that contradicts the Office's basis for asserting lack of utility may be sufficient to overcome any rejection for alleged lack of utility. *See* MPEP § 2107.02. Applicants herein submit the declaration of Randy Scott, Ph.D. (hereinafter the "Scott Declaration"), which rebuts the basis and logic of any *prima facie* showing of lack of utility, and which demonstrates that the asserted utility does not contravene any established scientific principles or beliefs. Specifically, the Scott Declaration is direct, objective evidence it is more likely than not true that the present claims are supported by Applicants' asserted utility for the claimed antibodies based on the disclosed and demonstrated PRO357 gene amplification. Dr. Scott is the Chairman and Chief Executive Officer of Genomic Health, Inc., in Redwood City, California. Genomic Health Inc. is a life science company founded in August 2000 and is engaged in "sophisticated genomic research to develop clinically validated molecular diagnostics." Paragraph 2 of the Scott Declaration. Dr. Scott clearly is an expert in the business of genomic information. For example, in 1991, Dr. Scott co-founded Incyte Pharmaceuticals, Inc., the world's first genomic information business. Under Dr. Scott's leadership, Incyte created the LifeSeq Gold® gene sequence and expression database, which is "an industry standard and the most comprehensive collection of biological information in the world." Paragraph 2 of the Scott Declaration. Dr. Scott's *Curriculum Vitae* is attached to and serves as part his declaration and clearly demonstrates that Dr. Scott is a qualified expert. In his declaration, Dr. Scott explains the success of the DNA microarray technology, which is similar to the real time-PCR technology used in measuring gene amplification of the present invention but allows for analysis of many genes at once rather than analysis of a single gene at a time:

> 7. The DNA microarray technology is based on hybridizing arrayed nucleic acid probes of known identity with target nucleic acid to determine the identity and/or expression levels (abundance) of target genes. DNA microarrays work by exploiting the ability of a given mRNA molecule to hybridize to the DNA template from which it originated. By using an array containing many

DNA samples, scientists can determine, in a single experiment, the expression levels of hundreds or thousands of genes within a sample by measuring the amount of mRNA bound to each site on the array. The amount of mRNA bound to the spots on the microarray is precisely measured, generating a profile of gene expression in the sample.

8. DNA microarray analysis has been extensively used in drug development and in diagnosis of various diseases. For instance, if a certain gene is over-expressed in a particular form of cancer relative to normal tissue, researchers use microarray chips to determine whether a drug candidate will reduce over-expression, and thereby cause cancer remission. In addition, if a gene has been identified to be over-expressed in a certain disease, such as a certain type of cancer, it can be used to diagnose that disease. Due to its importance in drug discovery and in the field of diagnostics, microarray technology has not only become a laboratory mainstay but also created a world-wide market of over $600 million in the year of 2005. A long line of companies, including Incyte, Affymetix, Agilent, Applied Biosystems, and Amersham Biosciences, made microarray technology a core of their business.

Dr. Scott further explains that the generally recognized and accepted correlation between gene amplification and protein overexpression is one reason for the success and wide-spread use of DNA microarray technology:

9. One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that <u>generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein.</u> Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels.

(Emphasis added). Thus, the Scott Declaration provides direct, objective evidence supporting Applicants' assertion of utility based on the accepted general correlation between gene amplification and protein overexpression. Applicants respectfully submit that the Scott Declaration is further evidence demonstrating that it is <u>more likely than not that the gene amplification of PRO357 correlates with protein overexpression of PRO357.</u>

In addition to the Scott Declaration, which provides direct evidence that generally mRNA levels correlate with protein levels, Applicants have submitted substantial evidence, for example the Goddard Declaration, demonstrating that the gene amplification observed for PRO357 is significant. However, the Office action mailed August 18, 2006 alleges that the Goddard Declaration is not persuasive evidence because the "specification fails to disclose the correlation between PRO357 polynucleotide amplification and PRO357 polypeptide expression or the significance of any such correlation." Page 4 of the Office action mailed 8/18/06. Applicants respectfully disagree. In particular, at Example 28 beginning on page 119 of the specification, Applicants teach:

> This example shows that the . . . PRO357- . . . encoding genes are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers. Therapeutic agents may take the form of antagonists of . . . PRO357 . . . polypeptide, for example, murine-human chimeric, humanized or human antibodies against a . . . PRO357 . . . polypeptide. These amplifications also are useful as diagnostic markers for the presence of a specific type of tumor type.

(Emphasis added). The underlined portion clearly discloses the correlation between PRO357 polynucleotide and PRO357 polypeptide – amplification of PRO357 polynucleotide is associated with overexpression of the gene product, PRO357 polypeptide. This passage also relays the significance of the correlation, *i.e.* that the polypeptides and antibodies may be used as therapeutic and diagnostic agents. Example 28 at page 137 further explains the significance of the correlation between gene amplification and protein overexpression:

> Because amplification of the DNAs tested occurs in various lung and colon tumors, it is highly probably that these DNAs play a significant role in tumor formation or growth. As a result, antagonists (*e.g.* antibodies) directed against the proteins encoded by the DNAs tested would be expected to have utility in cancer therapy and as useful diagnostic reagents. The polypeptides encoded by the DNAs tested have utility as diagnostic markers for determining the presence of tumor cells in lung and/or colon tissue samples.

The above-cited passages of the specification disclose both that the amplification of the PRO357 nucleic acid correlates with overexpression of the PRO357 polypeptide and that based on this relationship, PRO357 antibodies and polypeptides are useful as therapeutic and diagnostic agents. Thus, Applicants respectfully submit that no basis is provided for finding the Goddard Declaration unpersuasive.

Moreover, the Goddard Declaration is aimed at Dr. Goddard's opinion, as an expert in the field of cancer biology, that one of ordinary skill in the art would find it more likely than not that the data set forth in Table 10 at pages 125-127 of the specification indicates that the levels of PRO357 genomic DNA would be diagnostic of lung or colon cancer. Specifically, the Goddard Declaration illustrates the art acceptance of gene amplification data as an indicator of cancerous tissue. Thus, the Goddard Declaration provides persuasive evidence that the amplified PRO357 polynucleotide indicates the presence of cancer and therefore, polypeptides encoded by PRO357 and antibodies binding thereto are more likely than not to have significant utility as therapeutic and/or diagnostic agents.

Similar to the Scott Declaration submitted herewith, the Polakis Declarations (I and II) support a finding that in general there is an art accepted correlation between gene amplification in cancerous tissues and protein overexpression in cancerous tissues. Indeed, the second Polakis Declaration provides direct evidence that the project in which the PRO357 nucleic acid was first identified, the Tumor Antigen Project, has demonstrated a significantly high level of correlation between gene amplification and protein overexpression for genes identified in this project as being amplified in cancerous tissue compared to non-cancerous tissue. *See e.g.* Exhibit D of the second Polakis Declaration (of 31 genes identified as overexpressed in human tumor tissue compared to normal tissue at the mRNA level, 28 of them (*i.e.* greater than 90%) were overexpressed in human tumor tissue compared to normal human tissue at the protein level). The Office action mailed August 18, 2006 however argues that the Polakis Declarations are not persuasive because they are limited to a discussion of data regarding correlation of mRNA levels and protein levels, and not gene amplification levels and protein levels." Page 4 of the Office action mailed 8/18/06.

Applicants respectfully disagree that this is a sufficient basis for finding the Polakis Declarations unpersuasive. Specifically, gene amplification correlates with mRNA levels because mRNA is encoded by the nucleotides of the amplified gene. In turn, mRNA levels correlate with overexpression of the protein that is encoded by the mRNA. The correlation between gene amplification and mRNA levels is well-accepted. For example, Pollock and Orntoft demonstrate the art recognition of correlation between gene amplification and mRNA levels.

Pollack *et al.* profiled DNA copy number alterations across 6,691 mapped human genes in 44 breast tumors and 10 breast cancer cell lines and reported that microarray measurements of mRNA levels revealed remarkable degrees to which variation in gene copy number contributes to variation in gene expression in tumor cells. *See* Pollack *et al.*, "Microarray analysis reveals a major direct role of DNA copy number alteration in the transcriptional program of human breast tumors." 2002. *PNAS,* 99(20):12963-12968 (submitted herewith). Pollack *et al.* further report that their findings that DNA copy number plays a role in gene expression levels are generalizable. Thus significantly, "[t]hese findings provide evidence that widespread DNA copy number alteration can lead directly to global deregulation of gene expression, which may contribute to the development or progression of cancer."

In particular, Pollack *et al.* report a parallel analysis of DNA copy number and mRNA levels. Pollack *et al.* found that "[t]he overall patterns of gene amplification and elevated gene expression are *quite concordant, i.e.*, a significant fraction of highly amplified genes appear to be correspondingly highly expressed." (Emphasis added). Specifically, of 117 high-level DNA amplifications 62% were associated with at least moderately elevated mRNA levels and 42% were found associated with comparably highly elevated mRNA levels.

Orntoft *et al.* report similar findings in "Genome-wide study of gene copy numbers, transcripts, and protein levels in pairs of non-invasive and invasive human transitional cell carcinomas." 2002. *Molecular & Cellular Proteomics 1.1,* 37-45 (submitted herewith). Initially, Orntoft *et al.* note that "[h]igh throughput array studies of the breast

cancer cell line BT474 ha(ve) suggested that there is a correlation between DNA copy numbers and gene expression in highly amplified areas ( ), and studies of individual genes in solid tumors have revealed a good correlation between gene dose and mRNA or protein levels in the case of c-erb-B2, *cyclin d1, ems1,* and N-myc." Orntoft *et al.* note that their study reports a *striking correspondence* between DNA copy number, mRNA expression and protein expression. *See also* Hyman *et al.,* "Impact of DNA amplification on gene expression patterns in breast cancer." 2002. *Cancer Research*, 62:62-40-6245 (submitted herewith).

Thus, although the Polakis Declarations focus on the correlation between mRNA and protein overexpression, the data, scientific principles, and rules of correlation discussed in the Polakis Declarations are directly relevant to establishing the overall correlation between gene amplification and protein overexpression. This is particularly true because the Polakis Declarations discuss the correlation observed for genes identified in the Tumor Antigen Project, which is the project in which the PRO357 polynucleotide was identified. Thus, the Polakis Declarations discuss evidence that is highly relevant and related to PRO357 expression levels and patterns. Indeed, taken together, the Goddard Declaration demonstrates that PRO357 is amplified in lung or colon *cancer* tissues as compared to normal and the Polakis Declarations demonstrate that PRO357 polypeptide is more likely overexpressed in these cancerous tissues than not. This is persuasive evidence that the claimed antibodies to PRO357 are useful as diagnostics, and specifically are useful for diagnosing when cancer is more likely than not present in lung and/or colon tissues.

In support of its assertion that the Goddard and Polakis Declarations are unpersuasive, the Office action relies on two references - Pennica and Konopka. Specifically, the Office action alleges that "Pennica and Konopka provide evidence that the skilled artisan cannot assume that any one gene's amplification results in mRNA and polypeptide overexpression." Page 6 of the Office action mailed 8/18/06. However, it is not enough to show that for a particular gene a correlation does not exist. The law requires that the Office show evidence that it is more likely than not that such correlation, in general, does not exist. Such a showing has not been made.

Indeed, while Applicants acknowledge that there may be some instances where gene amplification does not correlate with protein overexpression (even the Scott Declaration acknowledges this point), Applicants respectfully maintain that absolute certainty is not required. Specifically, statistical certainty regarding an Applicants' assertion of utility is not required to satisfy 35 U.S.C. § 101. *Nelson v. Bowler,* 626 F.2d 853, 856-857, 205 USPQ 881, 883-884 (CCPA 1980). Moreover, where an Applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed as "wrong" even where there may be some reason to question the assertion. MPEP § 2107.02. Rather, a 35 U.S.C. § 101 rejection should only be sustained where the asserted utility violates a scientific principle or is *wholly* inconsistent with contemporary knowledge in the art. *In re Gazave,* 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (emphasis added).

Thus, even if Pennica and Konopka provide evidence of some instances where gene amplification does not correlate with protein overexpression these references alone do not demonstrate that the asserted utility violates a scientific principle, is wholly inconsistent with contemporary knowledge in the art, or make it more likely than not that a correlation between gene amplification and protein overexpression does not exist. Indeed, this is particularly true when the evidence is considered in its totality, as it must be. Specifically, the ample evidence submitted and relied on by Applicants, including the Scott, Polakis, and Goddard Declarations, and the numerous references discussed in the response submitted May 30, 2006, including Pollack, Orntoft, Hyman, Bermont, Varis, Hu, Papotti, Walmer, Janssens, Hahnel, Kammori, Bea, Maruyama, and Futcher, clearly demonstrates that instances when gene amplification does not correlate with protein overexpression are the exception and not the rule. The declarations submitted by and references cited by Applicants clearly establish that the contemporary knowledge in the art agrees with the scientific principle that gene amplification correlates with protein overexpression.

According to the Office action, "Pennica is evidence that not all gene amplifications are associated with overexpression of the corresponding gene product and that the skilled artisan would not have appreciated that PRO357 gene amplification, without more, would

have suggested a specific and substantial patentable utility for the PRO357 polypeptide and antibodies thereto." Page 7 of the Office action mailed 8/18/06.

Applicants respectfully disagree. Although Pennica may illustrate that increased copy number does not *necessarily* result in increased polypeptide expression, Pennica *et al.* does not teach that no correlation can be presumed. Moreover, as stated above, the standard for determining whether a correlation can be presumed is not absolute certainty. Rather, Applicants only must show that the existence of a correlation between gene amplification and protein overexpression is generally more likely than not. The fact that in Pennica, a case focused on a specific class of closely related molecules, there seemed to be no correlation with gene amplification and the level of mRNA/protein expression for one of the genes examined does not establish that it is more likely than not, in general, that such correlation does not exist. The Office action fails to show whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, as illustrated by the Scott and Polakis Declarations and the references previously cited by Applicants, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. *See, e.g.* Second Declaration of Paul Polakis. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . ." (Pennica *et al.*, page14722, left column, first full paragraph, emphasis added).

The Office action also questions Applicants' argument distinguishing Pennica, *i.e.* that "it is possible that the apparent amplification observed for *WISP-2* (in Pennica) may be caused by another gene in this amplicon." Page 7 of the Office action mailed 8/18/06. The Office action states that if this is correct, then it may be true that the gene amplification in the present application may fail to satisfy the utility requirements of 35 U.S.C. § 101 for the PRO357 polypeptide and polynucleotide. Page 7 of the Office action mailed 8/18/06.

Applicants respectfully disagree. The Office action misinterprets Applicants argument, which is based on statements in Pennica itself. Specifically, Applicants argument that *WISP-2* results reported by Pennica should be disregarded because the observed amplification might be caused by another gene comes directly from Pennica's characterization of the *WISP-2* gene amplification data:

> *WISP-2* DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. The gene for human *WISP-2* was localized to chromosome 20q12-20q13, at a region frequently amplified and associated with poor prognosis in node negative breast cancer and many colon cancers, suggesting the existence of one or more oncogenes at this locus (36-38). Because the center of the 20q13 amplicon has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon.

Pennica *et al* "*WISP* genes are members of the connective tissue growth factor family that are up-regulated in WNT-1 transformed cells and aberrantly expressed in human colon tumors." 1998. *PNAS:* 95:14717-14722, 14722. In contrast, Applicants teach in the specification that the procedures used for confirming amplification in the present invention strongly indicate that the "DNAs tested are responsible for the amplification of the particular region on the respective chromosome." Page 137, lines 13-20 of the specification. *See also* pages 134-137 of the specification for specific procedures used to confirm amplification of PRO357 DNAs, including epicenter mapping. Thus, the demonstrated gene amplification in the present specification does not fail to satisfy the utility requirement for any of the PRO357 polynucleotides, polypeptides, or antibodies.

Although Applicants disagree with the Office action's rejection of the Ashkenazi Declaration and characterization of the teachings of the Hanna reference, *see e.g.* Page 8 of the Office action mailed 8/18/06, Applicants respectfully submit that they need not rely this additional utility to support the claimed invention. MPEP § 2107 requires only "one credible assertion of a specific and substantial utility for each claimed invention to satisfy the utility requirement." (Emphasis added)). Applicants respectfully submit that the diagnostic (or therapeutic) utility of PRO357 polypeptides and antibodies is adequately asserted and supported by the substantial evidence discussed herein, which

demonstrates that in general it is more likely than not likely that gene amplification correlates with protein overexpression. The utility requirement of 35 U.S.C. § 101 does not require that this correlation be observed all the time or in all instances. Rather, 35 U.S.C. § 101 only requires that the correlation more likely exists than not exists. The Office has not provided evidence that outweighs the evidence submitted by Applicants, including declarations and reference articles, showing that more likely than not gene amplification correlates with protein overexpression.

2. Antibodies to PRO357 Polypeptides are Useful as Lung or Colon Therapeutics and/or Diagnostics

The Office action further asserts that even if PRO357 gene amplification correlates with PRO357 polypeptide overexpression, the claims still are not supported by an adequate utility because one of ordinary skill in the art would not know how to use the claimed antibodies in a practical way. Specifically, the Office action accepts, for the sake of argument, "that a person skilled in the art could derive some data regarding PRO357 polypeptide expression in tumors in which the PRO357 polynucleotide is amplified," and "that such data could be used to correlate PRO357 polypeptide expression with PRO357 polynucleotide amplification." Page 9 of the Office action mailed 8/18/06. However, the Office action alleges that even accepting these arguments, the utility requirement is not satisfied because "the specification provides no guidance to enable the skilled artisan to use data relating to PRO357 polypeptide expression in any practical way." Page 9 of the Office action mailed 8/18/06.

Applicants respectfully disagree. Specifically, at page 137 of the specification, Applicants explain that "[b]ecause amplification of the DNAs tested occurs in various lung and colon tumors, it is highly probable that these DNAs play a significant role in tumor formation or growth. As a result, antagonists (*e.g.* antibodies) directed against the proteins encoded by the DNAs tested would be expected to have utility in cancer therapy and as useful diagnostic reagents." Additionally, at page 119, the specification asserts that antibodies of PRO357 are useful as therapeutic and diagnostic agents based on the association between gene amplification and protein overexpression. Thus, the specification does

provide guidance for how the skilled artisan would use the data relating to PRO357 polypeptide expression in a practical way.

Further, the example provided in the Office action does not alter this. Specifically, the Office action posits that if PRO357 polypeptide were shown to be overexpressed in tissues where the PRO357 nucleic acid is not amplified, a skilled worked would not be enabled by the specification to use that information in any meaningful way. Applicants respectfully disagree that such a situation demonstrates the claimed invention is not supported by an adequate utility. As discussed above, the asserted utility for the claimed polypeptides and antibodies is based on an art acknowledged correlation between gene amplification and protein overexpression. Indeed, even the Office action accepts, "for the sake of argument," that such a correlation exists. The specification teaches that a polypeptide encoded by a gene amplified in cancerous tissues, and an antibody binding thereto, is useful as a therapeutic or diagnostic agent. The example provided in the Office action assumes a different set of facts. Specifically, it assumes that the polypeptide overexpression does not correlate with gene amplification. Such a relationship may or may not provide a utility sufficient to satisfy 35 U.S.C. § 101. However, that is irrelevant, because only a single utility is required and that utility is demonstrated by the correlation between gene amplification and protein overexpression. *See* MPEP § 2107 requiring only "one credible assertion of a specific and substantial utility for each claimed invention to satisfy the utility requirement." (Emphasis added)).

For the reasons given above, Applicants respectfully submit that consideration of the totality of the evidence clearly demonstrates that Applicants' asserted utility is specific, substantial, and credible. Applicants have overcome this ground of rejection and respectfully request it be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph:
Enablement

The Examiner contends that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art

would not know how to use the claimed invention. Applicants respectfully disagree. As discussed above, the claimed invention is adequately supported by an asserted utility that is both specific and substantial. Applicants respectfully request the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112 ¶1 for alleged inadequate disclosure on how to use the claimed invention.

CONCLUSION

Applicants believe this Request for Reconsideration fully responds to the Office Action. Applicants respectfully request the Examiner grant allowance of claims 22-26. The Examiner is invited to contact the undersigned attorney for the Applicant via telephone if such communication would expedite this application.

Applicants believe no fee is due in connection with the filing of this Request for Reconsideration, however, should any fees be deemed necessary for any reason relating to this paper, the Commissioner is hereby authorized to deduct said fees from Brinks Hofer Gilson & Lione Deposit Account No. 23-1925. A duplicate copy of this document is enclosed.

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